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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,527	07/10/2006	Jean-Philippe Girard	CNRS.001APC	2903

20995 7590 05/08/2009

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
05/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/539,527	GIRARD ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-26,28,30-35,37 and 127-129* is/are pending in the application.

4a) Of the above claim(s) *33-35,37 and 128* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26,28,30-32,127 and 129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-28-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on October 28, 2008 and April 2, 2009.

Currently, claims 23-26, 28, 30-35, 37, and 127-129 are pending in the instant application. Claims 33-35, 37, and 128 have previously been withdrawn as being drawn to non-elected inventions. Accordingly, claims 23-26, 28, 30-32, 127, and 129 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

Claims 23-26, 28, 30-32, and 127 remain rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement for the reasons of record as set forth in the Office action mailed on April 29, 2008 and for the reasons stated below.

Applicant's arguments filed on October 28, 2008 have been fully considered but they are not persuasive. Applicant argues that the instant specification fully complies with the written description requirement set forth in 35 U.S.C. 112, first paragraph because the specification provides a representative number of species to describe the claimed genus of "compounds" that inhibit NF-HEV polypeptide activity. In so arguing, applicant states that the specification provides nucleotide sequences (SEQ ID NOs:1-3) that encode each of NF-HEV polypeptides (SEQ ID NOs:4-6) together with "numerous" antisense and siRNA molecules that "can be constructed" based on the sequence information. First, it should be pointed out that the claims in the instant case are not merely drawn to a composition or product targeted to a nucleotide encoding NF-HEV. Rather, the claims are drawn to a therapeutic method comprising administering a nucleic acid compound (which is unidentified by the inventors of this case) that not only inhibits NF-HEV polypeptide activity but most importantly must result in treatment/amelioration effects for any chronic inflammation-associated diseases in a subject. If the claims were siRNA or antisense product claims, the disclosure of sequences might be sufficient to comply with the written description requirement. However, as the case law precedent makes clear, see *Univ. of Rochester v. G.D. Searle & Co.* (Fed. Cir 2004) already cited in the previous Office action, description of screening methods for a compound that may or may not indeed inhibit target activity in a subject does not suffice the written description requirement

for treatment methods. As such, the instantly claimed methods cannot be said to have been described as there is not even a single species of the generic nucleic acid compounds shown to inhibit NF-HEV polypeptide activity in a subject when administered, thereby ameliorating symptoms of chronic inflammation-related diseases.

Applicant further argues that the disclosure of "extensive chemical modifications" for improved *in vivo* activity shows that the inventors have described "a sufficient number of different compounds". It is questionable how applicant can possibly arrive at such conclusion when in fact there is no compound whatsoever disclosed in the specification. Clarification is required. Again, screening or optimizing methods that are merely and generically stated in the specification (mere disclosure of "how to obtain") do not represent the instantly claimed chronic inflammation-related disease treatment methods comprising administering a therapeutic compound that inhibits NF-HEV polypeptide activity.

In view of the foregoing, this rejection is maintained.

Claim Rejections - 35 USC § 102

Claims 23-25, 28, and 30 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ruben et al. for the reasons of record as set forth in the Office action mailed on April 29, 2008 and for the reasons stated below.

Applicant's arguments filed on October 28, 2008 have been fully considered but they are not persuasive. Applicant argues that Ruben et al. do not teach that the antisense compound of SEQ ID NO:35 is associated with inflammation-related diseases, nor do they teach a method step of identifying an individual having symptoms of chronic inflammation, and therefore the claims

are novel in view of Ruben et al. Contrary to applicant's argument, Ruben et al. expressly disclosed that antisense nucleic acids targeted to SEQ ID NO:35 is useful for diagnosing individuals having chronic inflammation diseases such as ulceretic disorders, thereby identifying individuals having inflammation diseases. See page 51. Further, it naturally and inherently flows that the method of Ruben et al. must necessarily comprise the method step of identifying a person having the inflammation disease symptoms because it is common sense to treat an individual having disease symptoms and therefore the treatment method of Ruben et al. implicitly and explicitly (diagnosing individuals having high expression of SEQ ID NO:35) comprises the step of identifying a diseased individual who needs treatment, followed by administering an antisense compound targeted to SEQ ID NO:35, absent evidence to the contrary. Hence, this rejection is maintained.

Claims 23-25, 28, 30-31, and 127 remain rejected under 35 U.S.C. 102(e) as being anticipated by Woolf et al. for the reasons of record as set forth in the Office action mailed on April 29, 2008 and for the reasons stated below.

Applicant's arguments filed on October 28, 2008 have been fully considered but they are not persuasive. Applicant argues that Jiang et al. teach SEQ ID NO:11450 is pain-related but do not teach that SEQ ID NO:437 is associated with chronic inflammation-related diseases, nor do they teach a method step of identifying an individual having symptoms of chronic inflammation, and therefore the claims are novel in view of Woolf et al. Contrary to applicant's argument, the claims are drawn to "ameliorating the ***symptoms*** of a condition associated with inflammation" in a subject having symptoms of chronic inflammation. As Woolf et al. have expressly disclosed,

antisense nucleic acid molecules targeted to SEQ ID NO:11450 (note that SEQ ID NO:11450 is identical to the NF-HEV nucleotide sequence of SEQ ID NO:1 that encodes SEQ ID NO:4 of the instant application) are useful for ameliorating "pain", which arises from inflammation. See paragraph 0111: "As used herein, "pain" refers to several different types of pain, including physiological or protective pain, inflammatory pain that occurs after tissue damage, and neuropathic pain which occurs after damage to the nervous system." See also paragraph 0119: "As used herein, "pain" can refer to "pain" experienced by an animal as a result of accidental trauma (e.g., falling trauma, burn trauma, toxic trauma, etc.), congenital deformity or malformation, infection (e.g., inflammatory pain)". See also paragraph 0003: "Pain is a state-dependent sensory experience which can be represented by a constellation of distinct types of pain including chronic pain, neuropathic pain, inflammatory pain, and physiological pain." Hence, the "pain" claimed to be treated in Woolf et al. is a symptom of a condition associated with chronic inflammation. Further, Woolf et al. taught a method of identifying individuals having pain symptoms and a method of treating pain in a subject in need thereof by administering an antisense or siRNA molecule targeted to SEQ ID NO:11450. See paragraphs 0112-0117 claims 44-48. Hence, not only did Woolf et al. teach a method of ameliorating a symptom of a chronic inflammation but they also taught a method of identifying subjects that need such amelioration/treatment. Further, it naturally and inherently flows that the any treatment/amelioration method must necessarily comprise the method step of identifying a subject having disease symptoms because it is common sense to treat an individual having disease symptoms, absent evidence to the contrary. In view of the foregoing, this rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 23-25, 28, 30-31, and 127 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kasuya et al. and Orr et al. for the reasons of record as set forth in the Office action mailed on April 29, 2008 and for the reasons stated below.

Applicant's arguments filed on October 28, 2008 have been fully considered but they are not persuasive. Applicant argues that the combination of Kasuya et al. and Orr et al. does not teach or suggest all the limitations of independent claim 23 because the association between DVS27 and chronic inflammation or the step of identifying a subject having chronic inflammation symptoms are not taught. Contrary to applicant's argument, Kasuya et al. clearly disclosed that DVS27 (note that the nucleotide sequence of DVS27 is identical to SEQ ID NO:1 of the instant application; the amino acid sequence of DVS27 is also identical to SEQ ID NO:4 claimed in the instant case) is "highly up-regulated in vasospastic arteries" and the up-regulated DVS27 expression are observed "in response to inflammatory stimuli". Further, Kasuya et al. expressly suggested that "the DVS27 gene was found to **encode a nuclear protein which could be involved in inflammatory events**." (emphasis added). See page 16, right column. Applicant's attention is also directed to the fact that NF-HEV is a nuclear protein that is described to be involved in inflammatory events. See paragraph 0007 of the instant specification. Further, the claims are not drawn to treating a "chronic" inflammatory condition as alleged by applicant. Applicant's attention is drawn to the claim language and the scope of the claimed methods. See for example the preamble of claim 23: "A method of ameliorating symptoms of **a condition associated with inflammation**"; see the final method step of claim 23: "thereby ameliorating symptoms of **a condition associated with inflammation**". Hence, the combination of Kasuya et

la. and Orr et al. renders the claimed invention obvious. In addition, Kasuya et al. cloned and identified DVS27 (or NF-HEV) from hemorrhagic cerebral vasospastic arteries and suggested that DVS27 (or NF-HEV) is involved in inflammation. With regard to the term "chronic inflammation" (see claim 23, lines 3-4), the specification merely states that "Provided herein is the characterization of NF-HEV, a nuclear factor expressed specifically in human endothelial cells from chronically inflamed tissues". See paragraph 0007 that is pointed out by applicant in support of the newly introduced claim limitation "chronic" inflammation. Furthermore, paragraph 0017 (also pointed out by applicant) teaches that "chronic inflammatory disorders typically involve development of HEV-like vessels", wherein "HEV-like vessels" are described as "high endothelial venules (HEVs)"-like vessels (see paragraph 0003). Hence, the fact that DVS27 (or NF-HEV) was known to be highly up-regulated in hemorrhagic cerebral vasospastic arteries clearly indicates to one of ordinary skill in the art that DVS27 of Kasuya et al. is involved in chronic inflammation because the specification taught that chronic inflammation involves high endothelial venules-like vessels. Applicant has not provided any contrary evidence showing that the hemorrhagic cerebral vasospastic arteries wherein DVS27 of Kasuya et al. is highly up-regulated and is responsible for inflammatory responses are not HEV-like vessels that are typically associated with chronic inflammatory disorders, nor has applicant articulated any reason that one of ordinary skill in the art would not use a nucleic acid inhibitor that inhibits inflammatory activities of DVS27 of Kasuya et al. in a subject having any kind of chronic inflammation disorder. Again, given the broadest reasonably interpretation of the term "chronic inflammation" in light of the teachings of the instant specification such that chronic inflammatory disorders typically involve HEV-like vessels, the teachings of Kasuya et al. that

DVS27 (again, identical to NF-HEV) is responsible for inflammatory events in hemorrhagic cerebral vasospastic arteries (thus HEV-like vessels) provide sufficient guidance/motivation to one of ordinary skill in the art to make an antisense agent against DVS27 and use it to reduce or ameliorate inflammatory responses in vasospastic arteries (HEV-like vessels) that are typically associated with chronic inflammation in a subject having symptoms of chronic inflammation, absent evidence to the contrary. Since applicant's arguments do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited, and since they do not show how the amendments avoid such references, this rejection is maintained.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 129 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claim is a new claim. Applicant has pointed out paragraph 0388 provide adequate support for the new claim. However, there does not appear to be a written description for the

claim limitation "providing an siRNA" in paragraph 0388 as alleged by applicant. See paragraph 0388 below:

[0388] In other embodiments of the present invention, the symptoms of a condition associated with inflammation are ameliorated by identifying a subject suffering from an inflammatory condition then modulating the level or activity of the NF-HEV polypeptide or a biologically active fragment thereof in the subject. In some embodiments, the subject is a human.

Accordingly, the claim limitation is considered to introduce new matter which is not adequately described in the application as originally filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 129 is rejected under 35 U.S.C. 102(e) as being anticipated by Woolf et al. (US 2007/0015145 A1, citation of record).

The claim is drawn to a method of ameliorating an inflammation condition comprising reducing NF-HEV activity by providing an siRNA complementary to at least a portion of a nucleic acid of NF-HEV.

Woolf et al. teach SEQ ID NO:11450, whose sequence is identical to the entire 2645 nucleotides of SEQ ID NO:1 encoding amino acids 1-270 of NF-HEV polypeptide of SEQ ID

NO:4. They teach that an antisense compound targeted to SEQ ID NO:11450 or any therapeutic agent which modulates the activity of the polypeptide encoded by SEQ DI NO:11450 is useful for ameliorating a subject's pain including chronic pain induced by inflammation. They teach that the therapeutic agent includes antisense agents and siRNA agents. See paragraphs 0003, 0066, 0068, 0262-0275, 0282-0287, 0417. Accordingly, all claim limitations are taught by Woolf et al.

Conclusion

No claim is allowed.

This application contains claims 33-35, 37, and 128 drawn to inventions nonelected with traverse in the reply filed on March 6, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635